201-15383

June 22, 2004

Michael O. Leavitt, Administrator
U.S. Environmental Protection Agency
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Comments on the HPV test plan for N-n-butylbenzenesulfonamide

Dear Administrator Leavitt:

The following comments on the test plan for N-n-butylbenzenesulfonamide (BBSA; CAS no. 3622-84-2), prepared by Proviron Fine Chemicals, are submitted on behalf of People for the Ethical Treatment of Animals, the Physicians Committee for Responsible Medicine, the Humane Society of the United States, the Doris Day Animal League, and Earth Island Institute. These animal, health, and environmental protection organizations have a combined membership of more than ten million Americans.

Proviron is proposing to conduct a combined repeated-dose, reproductive and developmental toxicity test (OECD no. 421) on BBSA. This will kill at least 675 animals. Yet the thoughtlessness with which Proviron's test plan has been prepared and with which this proposal has been made is astonishing.

First, the test plan mentions only four animal studies on BBSA (test plan references 2, 4, 5 and 11), three of which were carried out by Proviron itself. (Of the total of eleven references cited in the test plan, eight are in-house reports, two are non-specialist sources, and only one is the report of a study performed outside Proviron). However, numerous animal studies have in fact been carried out on BBSA (see, for example, Cho 1994, Duffield 1994, Haskell 1992a, 1992b, Lee 1995, Strong 1990a, 1990b, 1991a, 1991b, Wakayama 1992). These are not obscure studies, because since 1990 BBSA neurotoxicity has been a field of intense research (Cho 1994, Duffield 1994, Lee 1995, Nerurkar 1991, 1993, Strong 1990a, 1990b, 1991a, 1991b, Wakayama 1992). It is outrageous that Proviron does not appear to have made the slightest attempt to access any of the standard databases (e.g. ToxNet) for information about BBSA.

At least one study on the developmental toxicity of BBSA has been carried out, and it was found to be a developmental toxicant in mice, decreasing the number of live fetuses and causing deterioration in a range of fetal developmental indices (Hashimoto 1991). In addition, the repeated-dose study carried out by Proviron involved an assessment of male reproductive organs (IUPAC data set, p. 9), yet the test plan states that no reproductive toxicity studies have been carried out (p. 8).

It is quite clear that Proviron has made no attempt to abide by the following recommendation from the EPA: "In analyzing the adequacy of existing data, participants shall conduct a thoughtful, qualitative analysis rather than use a rote checklist approach. Participants may conclude that there is sufficient data, given the totality of what is known about a chemical,

including human experience, that certain endpoints need not be tested" and "as with all chemicals, before generating new information, participants should further consider whether any additional information obtained would be useful or relevant" (Wayland 1999; Federal Register 2000)

If the neurotoxicity and developmental toxicity of BBSA in animals were also to be found in humans, this would render its general toxicity purely academic and checking this box completely unnecessary. While beyond the scope of the HPV program, the crucial activities to be undertaken with respect to the toxicity of BBSA in humans are therefore (i) large-scale exposure and epidemiology studies, covering neurotoxicity, developmental toxicity and general toxicity; and/or (ii) practical reduction of occupational exposure by legal and technological means.

Secondly, Proviron carried out a 28-day oral toxicity study (OECD no. 407) during October and November 2003 (test plan, p. 7, IUCLID data set, p. 9), presumably while in the very process of preparing the test plan (submitted on December 29, 2003). This is a blatant violation of both the 1999 animal welfare agreement and the HPV framework agreement to which all HPV participants agreed to adhere. The EPA and the public are to be provided with the opportunity to comment on all test plans and sponsors are to consider those comments before any experimental work is undertaken. The 28-day study must have involved killing at least 40 mammals, and it was entirely pointless because the data obtained could be obtained from the OECD 421 test that Proviron has proposed.

Lastly, it is unclear which genetic toxicity test Proviron is proposing. On the one hand, Proviron states that it will carry out an *in vivo* genetic toxicity test (test plan, pp. 2, 3), but on the other hand, it states that it will carry out OECD test no. 473 (test plan, pp. 2, 8), which is an *in vitro* chromosomal aberration test. Proviron should clarify this point and should note that the EPA has stated that genetic toxicity tests should be conducted *in vitro* for the HPV program (Wayland 1999; Federal Register 2000). If Proviron does intend to use OECD test no. 473, the cells used should either be human lymphocytes or mammalian cells obtained from established cultures, so as to avoid killing additional animals in order to supply the cells.

In conclusion, the EPA must require Proviron to submit a revised test plan which complies with the original HPV framework agreement to which all participants agreed to adhere, including maximizing the use of existing data.

I would appreciate receiving a response to the specific issues raised in these comments from both the EPA and Proviron. I can be reached at 757-622-7382, ext. 8001, or via e-mail at JessicaS@peta.org.

Sincerely,

Jessica Sandler
Federal Agency Liaison

References

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